

Summary of the English translation of Japanese BA, BE Guidelines posted 2/29/12

English translation of the following 4 guidelines has been posted on the web (<http://www.nihs.go.jp/drug/DrugDiv-E.html>) and each one has its own separate Q&A document. Only the guidelines are summarized below, and not the Q&A documents. They are: 1) Guideline for Bioequivalence Studies of Generic Products; 2) Guideline for Bioequivalence Studies for Different Oral Solid Dosage Forms; 3) Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms, and; 4) Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms.

Overall Comment: All four are very easy to read and are well written with excellent scientific details. Also, there is a lot of very good and detailed material covered in these guidances and so you are strongly encouraged to read them and not rely only on the summary below!

Summary of Guideline #1: This is the biggest and most detailed guidance of the four (as a reference, it is similar to the General BA/BE Guidance that FDA published in 2003). It covers all the important aspects of BE for IR, ER, as well as non-oral dosage forms. The major areas covered for each of these are: reference and test products (with great deal of guidance on how to select the lot to be studied based on extensive dissolution results); BE studies; pharmacodynamic studies; clinical studies; dissolution tests, and; reporting of results. Of note is the definition of a poorly soluble drug product. A poorly soluble product is a drug product for which, when the test is performed at 50 rpm, the average dissolution rate of the reference product does not reach 85% at the testing time specified (2 hr at pH1.2 and 6 hr at other pHs) in any of the dissolution media specified (pH1.2, pH3-6.5, pH6.8-7.5, Water). Use of polysorbate 80 in the concentration range of 0.01% – 1.0% is recommended for studying the dissolution of products containing poorly soluble drugs. The most detail subsection is the 'BE studies' where all important and relevant aspects of a BE study design, conduct and analysis are covered well. The last section covers dosage forms for which BE studies are waived, namely IV aqueous injections. The two appendices cover f2 and time points to compare, and adjusting dissolution curves with lag times.

Summary of Guideline #2: This is just a 3 page guideline indicating that different oral solid dosage forms of the innovator products should undergo the same assessment as laid out in #1 above.

Summary of Guideline #3: This guideline covers what studies are needed for different strengths of IR and extended release products compared to the one(s) for which therapeutic efficacy and safety were established or BE to the innovator product was demonstrated via a human BE study; there is no specific mention of higher strengths. It covers topics of 'levels of formulation changes and required test', 'dissolution tests', and 'judgment of dissolution equivalence', along with appendices for 'f2 and time points for comparison', 'adjusting dissolution curves with lag times', 'method to evaluate effect of film coating on dissolution', and 'levels of formulations and required tests'. The levels of formulation changes range from Level A to Level E; levels of changes are defined in tables for levels B, C, and D. BE can be demonstrated based on extensive dissolution only, i.e., biowaivers can be granted, for changes up to Level D for non-narrow IR products, and up to Level C for non-narrow ER products. Table 3 also provides the list of 'Narrow Therapeutic Range Drugs'. For biowaivers, use of polysorbate 80 is restricted up to 0.1% for products containing poorly soluble drugs.

Summary of Guideline #4: This guideline is very similar to #3 except it deals with changes in formulations of IR and ER oral solid dosage forms. Also, as a reference, it is like the FDA SUPAC IR and MR guidance. It has the same sections and levels as #3 and biowaiver / BE based on dissolution can be granted up to Level D for non-narrow, soluble, rapidly dissolving IR product and up to Level C for non-narrow ER product.